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Increasing drug resistance of *Mycobacterium tuberculosis* in Sinaloa, Mexico, 1997–2005

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SUMMARY

Background: In 1997 the US Centers for Disease Control and Prevention (CDC) and the World Health Organization (WHO) reported high proportions of drug-resistant *Mycobacterium tuberculosis* in three Mexican states: Sinaloa, Baja California, and Oaxaca. In 2006, we showed that resistance to anti-tuberculosis drugs remained frequent in Sinaloa.
Objectives: The objectives of this study were to describe drug-resistant tuberculosis (TB) trends and to investigate the probability that patients acquire resistance to first-line anti-TB drugs on recurrence after treatment in Sinaloa.
Methods: Sputum specimens were collected from patients diagnosed with TB at all the health care institutions of Sinaloa during 1997–2005. Isolates were tested for susceptibility to first-line drugs.
Results: Among 671 isolates tested from 1997 to 2002, the overall resistance rate was 34.9% (95% confidence interval (CI) 31.2–38.4) with a 1.2% increase per year (Chi-square = 4.258, $p = 0.03906$). The prevalence of multi-drug resistance (MDR) was 17.9% (95% CI 14.9–20.7) with a 1.2% increase per year (Chi-square = 8.352, $p = 0.00385$). Of 50 patients registered twice between 1997 and 2005, 15 were fully susceptible at first registration, of whom six (40%) acquired drug resistance. Of 35 cases with any drug resistance at first registration, 21 (60%) came to acquire resistance to at least one other drug.
Conclusions: The proportion of drug-resistant TB increased during 1997–2005 in Sinaloa. Major efforts are needed to prevent the further rise and spread of drug-resistant and MDR TB.

1. Introduction

Despite efforts to control tuberculosis (TB), this disease continues to be one of the main public health problems in the world,[1,2] particularly in developing countries.[3,4] TB caused by *Mycobacterium tuberculosis* (*M. tuberculosis*) is one of the most important reemerging infectious diseases. Currently a third of the world's population is infected with *M. tuberculosis*,[5] and nearly 9 million new cases appear and 2 million deaths occur each year.[6] Furthermore, the emergence and spread of drug-resistant strains of *M. tuberculosis* reduce anti-TB treatment options and make the control of these infections difficult.[7–12] In 2006, extensively drug-resistant strains (XDR) were reported from several regions of the world; these present resistance even to second-line anti-TB treatment and represent a serious worsening of the epidemiological magnitude of TB worldwide.[13]

The World Health Organization (WHO) and the International Union Against Tuberculosis and Lung Diseases (IUATLD) have estimated that 50 million people worldwide are infected with drug-resistant (DR) *M. tuberculosis* strains, which present resistance to at least one of the first-line anti-TB drugs.[5,14] These organizations launched the Global Project on Anti-Tuberculosis Drug Resistance Surveillance, which uses standardized methods to measure the prevalence of drug resistance and assess its correlation with indicators of TB control.[3,14–16] Though the Global Project (WHO/IUATLD) has been operating since 1994, few countries and regions have reported data, and in some cases there have been discrepancies between the information reported by one organization and another.[17] Data from repeated surveys employing comparable methodologies over several years are essential to determine with any certainty in which direction the prevalence of drug resistance is moving.[16]

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Data from the global reports (WHO) on resistance to anti-TB drugs have shown that DR is present worldwide and that multidrug-resistant TB (MDR-TB; resistant at least to isoniazid and rifampin) is present in most of the world.[3] DR- and MDR-TB have been identified in Mexico,[4] despite the efforts of a National Tuberculosis Program based on the directly observed treatment strategy (DOTS). The US Centers for Disease Control and Prevention (CDC) and WHO/IUATLD (Global Project) reported high DR proportions in a unique national survey undertaken in 1997, covering three states in Mexico: Baja California, Oaxaca, and Sinaloa.[18]

In particular, moderate to high TB rates[19] have been found in Sinaloa, a state with approximately 2 534 000 inhabitants in the northwest of Mexico. Recently we reported that DR- and MDR-TB are still frequently found in this state and are associated with anti-TB treatment history.[20] Additional information is sorely needed in order to assist in the control of TB, the identification of future trends in DR and MDR, and the design of guidelines for the appropriate treatment of DR cases. Accordingly, the aim of this work was to analyze the behavior of *M. tuberculosis* (DR and MDR) in Sinaloa over time.

2. Materials and methods

The present study was based on an analysis of the results of susceptibility testing of *M. tuberculosis* strains isolated from patients with clinical symptoms or a diagnosis of pulmonary TB, whose cases were attended to at the Public Health Laboratory in Sinaloa, Mexico, from January 1997 through December 2005.

2.1. Data management and analysis

Patients were included from all the health care institutions of Sinaloa, with the majority coming from the SSA (Mexican Secretariat of Health) and IMSS (Mexican Institute of Health Care). We conducted three different stages of drug resistance analysis considering new cases, previously treated cases, and all TB cases. In the first stage, which focused on the period 1997–2002, we calculated the proportions of DR and MDR and analyzed trends in these over time. We did a follow-up in the second stage of the analysis for 2003–2004, calculating DR and MDR proportions and comparing these data with those of the period 1997–2002 (first stage). Finally, in a third stage of the analysis, we analyzed drug resistance data (DR and MDR) of re-registered TB patients from 1997 to 2005 (recurrent or chronic), selecting those patients with two isolates of *M. tuberculosis* in order to compare DR and MDR between the first and the second strains. Demographic data and treatment history were collected by the physician through patient interview.

2.2. Drug resistance definitions

We classified resistance to anti-TB drugs according to treatment history. The term 'new case' (resistance among new cases; primary resistance) refers to patients with pulmonary TB who had either never been treated with first-line anti-TB drugs or had received them for less than 1 month. A 'previously treated case' (resistance among previously treated cases; secondary or acquired resistance) refers to patients who had been treated for 1 month or more. 'All cases' (resistance among all cases; combined resistance) refers to all patients without considering their history of anti-TB treatment. We defined drug resistance (DR) as resistance to at least one of the first-line anti-TB drugs, and multi-drug resistance (MDR) as resistance to at least isoniazid (INH) and rifampin (RIF).

2.3. Laboratory methods

M. tuberculosis was isolated from sputa in Lowenstein–Jensen medium. Tests for drug susceptibility to INH, RIF, streptomycin (SM), ethambutol (EMB), and pyrazinamide (PZA) were carried out at the National Diagnostic and Epidemiologic Reference Institute (Mexico City) by use of the radiometric BACTEC 460 TB system (Becton Dickinson, Towson, MD, USA).

2.4. Statistical analysis

Statistical analysis was done with Epi-Info (version 6.04; CDC, Atlanta, GA, USA and WHO, Geneva, Switzerland). We carried out linear regression to evaluate DR and MDR trends, Chi-square to evaluate significance, and R^2 to indicate the proportion of variation. We also used odds ratios (OR) as a measure of association, and calculated confidence intervals to 95% (95% CI). We considered a p-value of <0.05 to be statistically significant.

3. Results

Drug resistance data for the period 1997–2005 were classified and analyzed as shown in Table 1. There were no important variations in age or sex of the patients across the stages studied.

3.1. Stage 1: DR and MDR magnitudes and their trends from 1997 to 2002

3.1.1. DR and MDR magnitudes from 1997 to 2002

The proportion of anti-TB drug resistance in all cases was calculated from 671 *M. tuberculosis* isolates; 234 (34.9%, 95% CI 31.2–38.4) showed resistance to at least one anti-TB drug (DR) and 120 (17.9%, 95% CI 14.9–20.7) showed resistance to at least INH and RIF (MDR) (Table 2). The frequency of anti-TB drug resistance was highest to INH and RIF, at 29.8% and 19.2%, respectively. Of all patients tested, 87.0% (584/671) informed the attending physician of their anti-TB treatment history.

Among the new cases (72.8%, 425/584), 90 (21.2%, 95% CI 17.3–25.0) showed DR and 21 (4.9%, 95% CI 2.8–7.0) showed MDR. The frequency of anti-TB drug resistance was highest to INH, SM, and RIF, at 17.2%, 11.3%, and 6.1%, respectively.

Table 1
Patient distribution by age, sex, and treatment history, according to study stage

Stage	Study/analysis	Patients			Sex (%)		Age (years)	
		New	Previously treated	All	Male	Female	Mean	Range
1; 1997–2002	Analysis of drug-resistant TB trends	425[a]	159[a]	671	66.8	33.2	40.9	10–91
2; 2003–2004	Comparison of drug-resistant TB; stages 1 and 2	40	26	66	63.6	36.4	41.2	13–76
3; 1997–2005	Analysis of drug-resistant TB in patients with recurrent disease who had two isolates of *M. tuberculosis*	15 (30 strains)	35 (70 strains)	50 (100 strains)	68	32	39.7	19–78

[a] Patients provided data on TB treatment history (87.0%; 584/671).

Table 2
Proportions of drug-resistant *Mycobacterium tuberculosis* for the periods 1997–2002 and 2003–2004; Sinaloa, Mexico

Tested *M. tuberculosis* strains	New cases (%)		Previously treated cases (%)		All cases (%)	
	1997–2002	2003–2004	1997–2002	2003–2004	1997–2002	2003–2004
Total tested	425	40	159	26	671	66
Fully sensitive	335 (78.8)	33 (82.5)	56 (35.2)	8 (30.8)	437 (65.1)	41 (62.1)
Any resistance (DR)	90 (21.2)	7 (17.5)	103 (64.8)	18 (69.2)	234 (34.9)	25 (37.9)
Isoniazid	73 (17.2)	0	94 (59.1)	18 (69.2)	200 (29.8)	18 (27.3)
Rifampin	26 (6.1)	0	80 (50.3)	12 (46.2)	129 (19.2)	12 (18.2)
Ethambutol	20 (40.7)	0	48 (30.2)	12 (46.2)	83 (12.4)	12 (18.2)
Streptomycin	48 (11.3)	7 (17.5)	52 (32.7)	7 (26.9)	122 (18.2)	14 (21.2)
Pyrazinamide	14 (3.3)	0	52 (32.7)	10 (38.5)	85 (12.7)	10 (15.2)
Multi-drug resistance (MDR)[a]	21 (4.9)	0	76 (47.8)	12 (46.2)	120 (17.9)	12 (18.2)
Number of drugs resistant to:						
1	41 (9.6)	7 (17.5)	13 (8.2)	3 (11.5)	68 (10.1)	10 (15.2)
2	24 (5.6)	0	22 (13.8)	1 (3.8)	52 (7.7)	1 (1.5)
3	13 (3.1)	0	25 (15.7)	4 (15.4)	44 (6.6)	4 (6.1)
4	7 (1.6)	0	21 (13.2)	8 (30.8)	35 (5.2)	8 (12.1)
5	5 (1.2)	0	22 (13.8)	2 (7.7)	35 (5.2)	2 (3.0)

[a] Resistance to at least isoniazid and rifampin.

Among previously treated cases (27.2%, 159/584), 103 (64.8%, 95% CI 57.3–72.1) showed DR and 76 (47.8%, 95% CI 40.0–55.5) showed MDR. INH and RIF were the drugs to which the highest resistance was found, at 59.1% and 50.3%, respectively (Table 2).

Notably, more than half of the patients with DR *M. tuberculosis* isolates showed MDR (51.3%; 120/234). Previously untreated patients showed *M. tuberculosis* isolates with a lower mean resistance (90/425; 21.2%) than the group of patients with a history of previous anti-TB treatment (103/159; 64.8%; Chi-square = 99.43, $p = 0.0000001$). Previous anti-TB treatment was associated with drug resistance (OR = 6.85).

3.1.2. DR and MDR trends from 1997 to 2002

DR and MDR in the 'all cases' patient group showed an increasing trend over time that turned out to be statistically significant (DR: 1.20% per year, Chi-square = 4.258, p trend = 0.03906; MDR: 1.22% per year, Chi-square = 8.352, p trend = 0.00385) (Figure 1). The differences in trends for the new cases and previously treated cases groups did not reach statistical significance.

3.2. Stage 2: Dynamics of drug resistance over time (2003–2004)

The proportions of DR and MDR in this period were both very similar to those found in the previous phase (1997–2002), although with some variations. For all cases in the period 2003–2004 there was 37.9% (25/66) DR and 18.2% (12/66) MDR, compared to 34.9% (234/671) DR and 17.9% (120/671) MDR during the period 1997–2002 (Table 2). Resistance to INH and RIF for 2003–2004 was 27.3% (18/66) and 18.2% (12/66), respectively, compared to 29.8% (200/671) and 19.2% (129/671), respectively, reported in the previous period.

Among previously treated cases during 2003–2004, DR and MDR were 69.2% (18/26) and 46.2% (12/26), respectively, while in the previous stage they were 64.8% (103/159) and 47.8% (76/159), respectively. Resistance to INH increased from 59.1% (94/159) to 69.2% (18/26), while that to RIF decreased from 50.3% (80/159) to 46.2% (12/26). Among new cases, DR decreased from 21.2% (90/425) to 17.5% (7/40), while MDR and anti-TB drug resistance to INH and RIF decreased to 0% (Table 2).

3.3. Stage 3: Evaluation of DR and MDR among re-registered TB patients from 1997 to 2005

For the period 1997–2005 we found 50 TB patients with two isolates of *M. tuberculosis* (100 isolates total), of whom 70% (35/50) had received treatment for TB and 30% (15/50) had not (Table 3).

Among new cases (15 patients, 30 isolates), there were important increases in DR (26.7%) and MDR (40%). The highest increases were to INH (40%) and RIF (33.3%). Drug resistance to only one drug declined 20%, but resistance to two drugs increased 6.7%, to three drugs increased 33.3%, and to four drugs increased 6.7%. Resistance to five drugs remained constant (0% change) at 6.7%.

Among previously treated cases (35 patients, 70 isolates), there were moderate increases in DR (2.9%) and MDR (8.6%). The highest increases in resistance were to EMB (40%) and PZA (37.1%). There was a decrease in resistance to one drug of 11.4%, to two drugs of 5.7%, and to three drugs of 11.4%. Resistance to four drugs

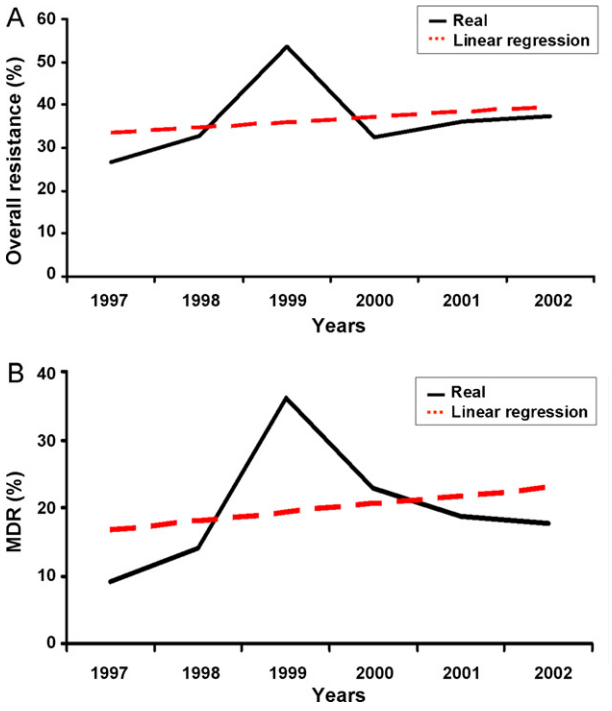

Figure 1. Trends in multi-drug resistance (MDR) and overall resistance (DR) in *Mycobacterium tuberculosis*; Sinaloa, Mexico, 1997–2002. (A) Trend in overall resistance (%) among all tuberculosis cases (DR). Chi-square for linear trend = 4.258, $p = 0.03906$. Linear regression formula: $R^2 = 0.0593$, X-coefficient, 1.2017. (B) Trend in MDR (%) among all tuberculosis cases. Chi-square for linear trend = 8.352, $p = 0.00385$. Linear regression formula: $R^2 = 0.0616$, X-coefficient, 1.2263.

Table 3
Drug resistance in the first and second *Mycobacterium tuberculosis* isolates; Sinaloa, Mexico, 1997–2005

Anti-TB drugs	*M. tuberculosis* (%)								
	First isolate			Second isolate			Difference		
	New cases ($n=15$)	Previously treated cases ($n=35$)	All cases ($n=50$)	New cases ($n=15$)	Previously treated cases ($n=35$)	All cases ($n=50$)	New cases ($n=15$)	Previously treated cases ($n=35$)	All cases ($n=50$)
Isoniazid	2 (13.3)	28 (80)	30 (60)	8 (53.3)	31 (88.6)	39 (78)	6 (40)	3 (8.6)	9 (18)
Rifampin	2 (13.3)	24 (68.6)	26 (52)	7 (46.7)	26 (74.3)	33 (66)	5 (33.3)	2 (5.7)	7 (14)
Pyrazinamide	1 (6.7)	12 (34.3)	13 (26)	4 (26.7)	25 (71.4)	29 (58)	3 (20)	13 (37.1)	16 (32)
Ethambutol	1 (6.7)	11 (31.4)	12 (24)	3 (20)	25 (71.4)	28 (56)	2 (13.3)	14 (40)	16 (32)
Streptomycin	2 (13.3)	16 (45.7)	18 (36)	4 (26.7)	20 (57.1)	24 (48)	2 (13.3)	4 (11.4)	6 (12)
Any resistance (DR)	4 (26.7)	31 (88.6)	35 (70)	8 (53.3)	32 (91.4)	40 (80)	4 (26.7)	1 (2.9)	5 (10)
Multi-drug resistance (MDR)[a]	1 (6.7)	22 (62.9)	23 (46)	7 (46.7)	25 (71.4)	32 (64)	6 (40)	3 (8.6)	9 (18)
Number of drugs resistant to:									
1 drug	3 (20)	4 (11.4)	7 (14)	0	0	0	−3 (−20)	−4 (−11.4)	−7 (−14)
2 drugs	0	7 (20)	7 (14)	1 (6.7)	5 (14.3)	6 (12)	1 (6.7)	−2 (−5.7)	−1 (−2)
3 drugs	0	10 (28.6)	10 (20)	5 (33.3)	6 (17.1)	11 (22)	5 (33.3)	−4 (−11.4)	1 (2)
4 drugs	0	6 (17.1)	6 (12)	1 (6.7)	6 (17.1)	7 (14)	1 (6.7)	0	1 (2)
5 drugs	1 (6.7)	4 (11.4)	5 (10)	1 (6.7)	15 (42.9)	16 (32)	0	11 (31.4)	11 (22)

[a] Resistance to at least isoniazid and rifampin.

remained constant (0% change) at 17.1%, but there was a 31.4% increase in resistance to five drugs.

Among all cases (50 patients, 100 isolates), DR increased 10% and MDR 18%. The highest increases were to EMB and PZA, both 32%. Decreases in resistance were found to one drug (14%) and to two drugs (2%), while there was a 2% increase in resistance to three drugs and to four drugs, and a 22% increase in resistance to five drugs (Table 3).

In relation to the second isolate (of 50 patients with two isolates), 18% (9/50) remained free of drug resistance, 12% (6/50) became DR, 26% (13/50) showed the same resistance level, and 42% (21/50) showed higher resistance. Of the latter group, resistance increased to one drug (42.9%; 9/21), two drugs (47.6%; 10/21), and three drugs (9.5%; 2/21). Of those who had the same resistance level in both isolates (26%; 13/50), 38.5% (5/13) showed resistance to five drugs.

4. Discussion

In spite of the fact that there is a National Control Program in Mexico, TB continues to be a public health problem. Previous reports have indicated a high prevalence of drug resistance in some Mexican populations.[4,11,18,20–25] In the 6 years from 1997 to 2002, we found that 34.9% of *M. tuberculosis* isolates in Sinaloa were resistant to one or more first-line anti-tuberculosis drugs (DR), with 17.9% resistant to both INH and RIF (MDR), with an increasing trend in both of these categories.

The overall resistance rate found in this study (34.9%) was higher than that found in the unique national survey (21.5%) carried out by the Mexican Secretariat of Health and the CDC in 1997 in three states of Mexico (Baja California, Oaxaca, and Sinaloa),[18] and higher than the median rate (20%) reported for the Global Project (WHO/IUATLD).[3] Furthermore, the DR level in Sinaloa was also higher than that found in several other states: in Mexico State and Mexico City (30.0%; 1991–1993),[25] in Veracruz (25%; 1995–1999),[12] and in Baja California (25.8%; 1998–1999).[23] Moreover, the result of the present study was almost the same as that reported in San Luis Potosi (36.0%; 2003–2004),[22] but was lower than that reported in Chiapas (72.2%; 1992)[26] and Baja California (41%; 1995–1996).[27]

In this study, the MDR rate (17.9%) was higher than that determined in the unique national survey (7.4%),[18] and higher than the median rate from the WHO/IUATLD Global Project (5.3%).[3] This MDR level in Sinaloa was also higher than that found in two other states: in Veracruz (6.2%; 1995–1999)[3,12] and in Baja California (13.3%).[23] Moreover, it was very similar to that found in San Luis Potosi (16%; 2003–2004),[22] but was lower than that reported in Mexico State and Mexico City (64.0%)[25] and Chiapas (53.0%).[26] It is very worrisome to note the high level of MDR among DR cases, and that trends of DR and MDR (from 1997 to 2002) showed a statistically significant increase (1.2% per year; Figure 1). Equally alarming is that the highest levels of drug resistance were for INH (29.8%) and RIF (19.2%, Table 2), as these are the most potent anti-TB drugs for primary treatment as suggested by the WHO.

Among new cases from 1997 to 2002, DR was higher (21.2%) than that reported by the national survey (12.9%)[18] and by all the other Mexican studies considered, although it was similar to that found in Veracruz (20.7%; 1995–1998).[11] MDR (4.9%) was also higher than that found in all the other Mexican studies considered, except for the rate found in Baja California (10%; 1995–1996)[27] and in Mexico State and Mexico City (6.0%; 1991–1993).[25] Among previously treated cases from 1997 to 2002, DR (64.8%) and MDR (47.8%) rates were higher than those reported nationally (50.5% and 22.4%, respectively)[18] and in all other studies in Mexican populations mentioned: in Mexico State and Mexico City (46.0% and 35.0%, respectively),[25] in Veracruz (49.2% and 23.8%, respectively),[11] and in Baja California (48.9% and 30.6%, respectively).[23] These data suggest that in Sinaloa, DR *M. tuberculosis* is becoming a grave problem, even graver if we consider that for practical purposes the presence of resistant strains of *M. tuberculosis* in a community is always a consequence of inadequate TB treatment.[8] In agreement with this observation is the fact that among previously treated cases, 64.8% of patients had DR and 47.8% MDR.

Drug resistance levels in the follow-up phase (2003–2004) generally remained moderate or high. However, it is important to mention that there were decreases in the levels of DR (21.2% to 17.5%) and MDR (4.9% to 0.0%) among new cases. This could be explained by the decrease in cases studied in this stage and/or by a better population control of TB treatment. The latter would suggest an intermittent control of the Sinaloa drug-resistant TB during this period.

In the third stage of the analysis where we compared the resistance profiles of a group of patients with two strains of *M. tuberculosis* (recurrent or chronic patients) from 1997 to 2005, there were important increases in drug resistance in the second

strain compared to the first. There was an overall worsening of drug resistance among all patients: 12% (6/50) of all patients became DR and 60% (21/35) patients with some form of drug resistance developed greater resistance profiles. These increases resulting from the periodic evaluation of susceptibility show that there could be important treatment failure and relapse in these patients, perhaps because of inadequate or discontinuous treatment, suggesting a poor control of TB at the population level.

In conclusion, the results of this study for the period 1997–2005 in Sinaloa reveal moderate or high levels of drug resistance compared with the unique national survey,[18] the WHO/IUATLD Global Project (Report No. 4; 2008),[3] and other previous studies in Mexican populations,[4] with trends towards an increase in drug resistance. Although the findings from the unique national survey of 1997, which included the state of Sinaloa,[18] led to a limitation of increases in drug resistance by the addition of EMB to the TB treatment regimen (INH/RIF/EMB/PZA (RIPE) in new case-patients, from the year 2000),[28] the relatively high prevalence of MDR and the increasing rates of EMB resistance found in the later years of the present study (Tables 2 and 3), suggest a chronic public health problem that, if not contained rapidly, may be out of control in coming years.

This suggests that continuous efforts should be directed at the prevention of TB and the effective application of TB control programs (DOTS strategy) in Sinaloa. The latter strategy is vital, as treatment failure and relapse, perhaps because of inadequate or discontinuous treatment, is probably an important factor in the patients studied. The probable poor control of TB at the population level is consistent with the high levels of resistance occurring among previously treated cases. However, there are other possible factors, such as acquired resistance and transmitted primary resistance. Therefore, the magnitude of potential failure and relapse suggested in this study does not allow for definitive conclusions to be drawn on the TB control program.

The limitations of the current study include possible biases that could limit the validity of results, such as the methods of patient selection and data collection, including data related to treatment history, which was used to differentiate between new and previously treated cases. On the other hand, our study sample consisted of all strains of *M. tuberculosis* from TB patients at the only mycobacterial laboratory of Sinaloa State, which ensures some representation of this population. Thus despite possible limitations, the current study strongly suggests problems in the control of TB drug resistance in the Sinaloa population.

This is the first study reporting data on drug resistance trends in Sinaloa in relation to the current regimens of TB treatment (RIPE in new case-patients), and represents a follow-up of the national survey of 1997 (Baja California, Oaxaca, and Sinaloa).[18] Finally, in accordance with the WHO/IUATLD (Report No. 4, 2008),[3] Mexico has started a nationwide survey and has plans to test MDR-TB isolates for second-line drug resistance at a supranational reference laboratory. This survey must be considered a priority for the planning of the future management of MDR-TB and probably XDR-TB in Mexico.

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Conflict of interest: No conflict of interest to declare.

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